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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/732,919 | 12/10/2003 | David J. Yang | UTSC:841US/10314647 | 7351 |

32425 7590 12/04/2009

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| EXAMINER | |
|---|---|
| SCHLIENTZ, LEAH H | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1618 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 12/04/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/732,919 | YANG ET AL. | |
| | Examiner | Art Unit | |
| | Leah Schlientz | 1618 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *2,5,14-17,23,25-28,31-51,60 and 61* is/are pending in the application.

4a) Of the above claim(s) *5,14-17,23,25-28 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,31-33,35-51 60 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/18/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Acknowledgement of Receipt*

Applicant's Response, filed 8/28/2009, in reply to the Office Action mailed 4/8/2009, is acknowledged and has been entered. Claims 2, 5, 14-17, 23, 25-28, 31-51, 60 and 61 are pending, of which claims 5, 14-17, 23, 25-28 and 34 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 2 and 60 have been amended. Claims 2, 31-33, 35-51, 60 and 61 are readable upon the elected invention and are examined herein on the merits for patentability.

### *Information Disclosure Statement*

The information disclosure statement (IDS) submitted on 6/18/2009 was filed after the mailing date of the Office Action on 4/8/2009. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

### *Response to Arguments*

The double patenting rejections have been withdrawn in view of the terminal disclaimer filed 8/28/2009.

Any rejection not reiterated herein has been withdrawn as being overcome by amendment.

Applicant's arguments have been fully considered but they are not persuasive for reasons set forth hereinbelow.

***Declaration under 37 CFR 1.132***

The declaration of Jerry Bryant under 37 CFR 1.132 filed 8/28/2009 is insufficient to overcome the rejection of claims 2, 31-33, 35-51, 60 and 61 based upon 35 U.S.C. 103(a) as set forth in the last Office action because: while the opinion of inventor Bryant set forth in the declaration has been fully considered, the opinion set forth therein does not take the place of actual proof, in order to address 99m-Tc-EC-aminopencivir as a substrate for HSV-1 thymidine kinase.

**MPEP 716.01(c) Probative Value of Objective Evidence [R-2]**

**I. TO BE OF PROBATIVE VALUE, ANY OBJECTIVE EVIDENCE SHOULD BE SUPPORTED BY ACTUAL PROOF**

Objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See, for example, *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984) ("It is well settled that unexpected results must be established by factual evidence." "[A]ppellants have not presented any experimental data showing that prior heat-shrinkable articles split. Due to the absence of tests comparing appellant's heat shrinkable articles with those of the closest prior art, we conclude that appellant's assertions of unexpected results constitute mere argument."). See also *In re Lindner*, 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972); *Ex parte George*, 21 USPQ2d 1058 (Bd. Pat. App. & Inter. 1991).

**III. OPINION EVIDENCE**

Although factual evidence is preferable to opinion testimony, such testimony is entitled to consideration and some weight so long as the opinion is not on the ultimate legal conclusion at issue. While an opinion as to a legal conclusion is not entitled to any

weight, the underlying basis for the opinion may be persuasive. *In re Chilowsky*, 306 F.2d 908, 134 USPQ 515 (CCPA 1962) (expert opinion that an application meets the requirements of 35 U.S.C. 112 is not entitled to any weight; however, facts supporting a basis for deciding that the specification complies with 35 U.S.C. 112 are entitled to some weight); *In re Lindell*, 385 F.2d 453, 155 USPQ 521 (CCPA 1967) (Although an affiant's or declarant's opinion on the ultimate legal issue is not evidence in the case, "some weight ought to be given to a persuasively supported statement of one skilled in the art on what was not obvious to him." 385 F.2d at 456, 155 USPQ at 524 (emphasis in original)).

In assessing the probative value of an expert opinion, the examiner must consider the nature of the matter sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985), *cert. denied*, 475 U.S. 1017 (1986). See also *In re Oelrich*, 579 F.2d 86, 198 USPQ 210 (CCPA 1978) (factually based expert opinions on the level of ordinary skill in the art were sufficient to rebut the *prima facie* case of obviousness); *Ex parte Gray*, 10 USPQ2d 1922 (Bd. Pat. App. & Inter. 1989) (statement in publication dismissing the "preliminary identification of a human b-NGF-like molecule" in the prior art, even if considered to be an expert opinion, was inadequate to overcome the rejection based on that prior art because there was no factual evidence supporting the statement); *In re Carroll*, 601 F.2d 1184, 202 USPQ 571 (CCPA 1979) (expert opinion on what the prior art taught, supported by documentary evidence and formulated prior to the making of the claimed invention, received considerable deference); *In re Beattie*, 974 F.2d 1309, 24 USPQ2d 1040 (Fed. Cir. 1992) (declarations of seven persons skilled in the art offering opinion evidence praising the merits of the claimed invention were found to have little value because of a lack of factual support); *Ex parte George*, 21 USPQ2d 1058 (Bd. Pat. App. & Inter. 1991) (conclusory statements that results were "unexpected," unsupported by objective factual evidence, were considered but were not found to be of substantial evidentiary value).

Although an affidavit or declaration which states only conclusions may have some probative value, such an affidavit or declaration may have little weight when considered in light of all the evidence of record in the application. *In re Brandstadter*, 484 F.2d 1395, 179 USPQ 286 (CCPA 1973).

An affidavit of an applicant as to the advantages of his or her claimed invention, while less persuasive than that of a disinterested person, cannot be disregarded for this reason alone. *Ex parte Keyes*, 214 USPQ 579 (Bd. App. 1982); *In re McKenna*, 203 F.2d 717, 97 USPQ 348 (CCPA 1953).

In the instant case, the declaration asserts that "a person of ordinary skill in the art would not be motivated to substitute the 18F labeled penciclovir probe of Iyer et al.

with 99mTc-EC-aminopenciclovir because it is highly unlikely that 99mTc-EC-aminopenciclovir would be suitable for imaging HSV-1 thymidine kinase reporter gene expression since it would not be a substrate for HSV-1 thymidine kinase." The declaration recites that the prior art teaches that the acyclic side chain of guanoside analogues such as penciclovir and acyclovir were known to substitute for sugar moieties, and that the side chain of Tc-EC-aminopencivlovir does not structurally resemble a sugar moiety or any part of a sugar moiety by virtue of inclusion of the amino modification of penciclovir and by virtue of binding of EC to the amino moiety of aminopenciclovir. Applicant asserts that the importance of structural similarity of the side chain to sugar moities can be found in Exhibits 1-3. The declaration asserts that a number of acyclic guanisine analogues were known in the field at the time of the filing date of the present patent application, and these structural analogues were known to have acyclic side chains that include at least a portion of a sugar moiety, citing Exhibits 4-6.

However, inventor Bryant's opinion that it is highly unlikely that 99mTc-EC-aminopenciclovir would be suitable for imaging HSV-1 thymidine kinase reporter gene expression since it would not be a substrate for HSV-1 thymidine kinase has not been supported by actual proof. In the instant case, Iyer specifically teaches that FPCV is a substrate for HSV1-TK in vitro (page 99), and that in living animals, HSV1-tk reporter gene expression can be monitored by the HSV1-tk/FPCV PET reporter gene-PET reporter probe system (page 101). The FPCV has no sugar on the side chain, yet FPCV is a substrate for HSV1-TK. Therefore, the assertion that Tc-EC-

aminopencivlovir is lacking a sugar moiety on the side chain and would be an unlikely substrate for HSV-1 thymidine kinase is not persuasive, since it is clear that the presence of a sugar moiety on the side chain is not required for a given probe to be a substrate for HSV1-TK, as evidenced by FPCV. In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 31-33, 35-48, 51, 60 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iyer (J. Nucl. Med., 2001, 42, p. 96-105) in view of Zareneyrizi (Anti-Cancer Drugs, 1999, 10, p. 685-692), further in view of Yang (Ann. Nucl. Med. Sci., 2000, 13, p. 19-36), for reasons set forth in the previous Office Action.

Claims 2, 31-33, 35-51, 60 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iyer (J. Nucl. Med., 2001, 42, p. 96-105) in view of Zareneyrizi (Anti-Cancer Drugs, 1999, 10, p. 685-692)and Yang (Ann. Nucl. Med. Sci., 2000, 13, p. 19-

36), further in view of Belinka (US 5,609,847) for reasons set forth in the previous Office Action.

Applicant argues on pages 10-11 that the Examiner has failed to establish a prima facie case of obviousness because the Examiner has not set forth sufficient reason with rational underpinning as required by KSR to support a prima facie case of obviousness. Applicant asserts that Iyer teaches 18F labeling of penciclovir, and that there is no rational basis as to why one of ordinary skill would be motivated to replace the 18F of Iyer with 99mTc-EC of Zarenyrizi. Applicant further argues that Iyer teaches that the lack of an ether oxygen in the side chain of PCV has a significant effect on its biological properties, and asserts that Iyer actually teaches away from substituting a single atom radiolabel with a substantially larger moiety such as 99mTc-EC.

This is not found to be persuasive. Motivation for substitution of 18F can be readily found in Zarenyrizi and Yang. For example, Zareneyirizi and Yang teach that $^{99m}$Tc labeling of radiopharmaceuticals is preferred because of favorable physical characteristics as well as extremely low price compared to $^{18}$F (page 685). One would have had a reasonable expectation of success in providing $^{99m}$Tc in an ethylenedicysteine carrier, as Zareneyirizi and Yang teach that such complexes form stable chelates with oxotechnetium. Applicant's arguments regarding Iyer single atom radiolabels have been fully considered. However, it is deemed that the Iyer reference does not reach the level of a teaching away from substitution of $^{99m}$Tc-EC for $^{18}$F, as suggested by Applicant. A prior art reference that "teaches away" from the claimed

invention is a significant factor to be considered in determining obviousness; however, "the nature of the teaching is highly relevant and must be weighed in substance. A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994) (Claims were directed to an epoxy resin based printed circuit material. A prior art reference disclosed a polyester-imide resin based printed circuit material, and taught that although epoxy resin based materials have acceptable stability and some degree of flexibility, they are inferior to polyester-imide resin based materials. The court held the claims would have been obvious over the prior art because the reference taught epoxy resin based material was useful for applicant's purpose, applicant did not distinguish the claimed epoxy from the prior art epoxy, and applicant asserted no discovery beyond what was known to the art.). Furthermore, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed...." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). See MPEP 2145. In the instant case, the Iyer reference merely teaches that slight structural modifications may affect biological activity, and thus it is considered that Iyer does not specifically discredit or discourage some degree of structural modification, such as by conjugation of a chelating moiety.

Applicant further argues on pages 12-14 of the Response that 99mTc-EC-penciclovir would not likely be suitable for imaging HSV1-thymidine kinase reporter

gene expression as required by Iyer since it would not be a substrate for HSV1-thymidine kinase, citing the declaration of Jerry Bryant.

This is not found to be persuasive. While the opinion of inventor Bryant set forth in the declaration has been fully considered, the opinion set forth therein does not take the place of actual proof, in order to address 99m-Tc-EC-aminopencivir as a substrate for HSV-1 thymidine kinase. The declaration asserts that "a person of ordinary skill in the art would not be motivated to substitute the 18F labeled penciclovir probe of Iyer et al. with 99mTc-EC-aminopenciclovir because it is highly unlikely that 99mTc-EC-aminopenciclovir would be suitable for imaging HSV-1 thymidine kinase reporter gene expression since it would not be a substrate for HSV-1 thymidine kinase." The declaration recites that the prior art teaches that the acyclic side chain of guanoside analogues such as penciclovir and acyclovir were known to substitute for sugar moieties, and that the side chain of Tc-EC-aminopencivlovir does not structurally resemble a sugar moiety or any part of a sugar moiety by virtue of inclusion of the amino modification of penciclovir and by virtue of binding of EC to the amino moiety of aminopenciclovir. Applicant asserts that the importance of structural similarity of the side chain to sugar moities can be found in Exhibits 1-3. The declaration asserts that a number of acyclic guanisine analogues were known in the field at the time of the filing date of the present patent application, and these structural analogues were known to have acyclic side chains that include at least a portion of a sugar moiety, citing Exhibits 4-6.

However, inventor Bryant's opinion that it is highly unlikely that 99mTc-EC-aminopenciclovir would be suitable for imaging HSV-1 thymidine kinase reporter gene expression since it would not be a substrate for HSV-1 thymidine kinase has not been supported by actual proof. In the instant case, Iyer specifically teaches that FPCV is a substrate for HSV1-TK in vitro (page 99), and that in living animals, HSV1-tk reporter gene expression can be monitored by the HSV1-tk/FPCV PET reporter gene-PET reporter probe system (page 101). The FPCV has no sugar on the side chain, yet FPCV is a substrate for HSV1-TK. Therefore, the assertion that Tc-EC-aminopencivlovir is lacking a sugar moiety on the side chain and would be an unlikely substrate for HSV-1 thymidine kinase is not persuasive, since it is clear that the presence of a sugar moiety on the side chain is not required for a given probe to be a substrate for HSV1-TK, as evidenced by FPCV. In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

***Conclusion***

No claims are allowed at this time.

Although Applicant's arguments as set forth in the aforementioned Response have been fully considered, they are deemed unpersuasive. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is (571)272-9928. The examiner can normally be reached on Monday-Tuesday and Thursday-Friday 9 AM-5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS